Claims 1, 5, and 6 are amended, and claims 26-30 are added; as a result, claims 1-9 and 26-30 are now pending in this application.

The amendments to the claims are supported throughout the originally filed specification and claims. Amended claims 1, 5, and 6 are supported, e.g., by the corresponding originally filed claims. New claim 26 is supported, e.g., by originally filed claim 1 and at page 10, lines 28 to 30. New claim 27 is supported, e.g., at page 11, line 6. New claim 28 is supported, e.g., by originally filed claim 1. New claims 29 and 30 are supported, e.g., by originally filed claim 1 and at page 11, lines 11-13. As such, no new matter has been added by way of this amendment.

The amendments of claims 1, 5, and 6 herein have been made to clarify the claims and do not narrow the scope of the claims. Accordingly, Applicants are entitled to a full range of equivalents upon issuance of the instant claims.

The 35 U.S.C. § 112, Second Paragraph, Rejections of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. These rejections are respectfully traversed.

The Examiner stated that the term "and/or" in claim 1 was confusing. The term has been deleted and the claim amended to clarify the claim. The Examiner stated that claim 5 was confusing as to whether more than one adjunctive compound is required. The Examiner suggested amending it to recite "an antidepressant, an analgesic, . . ." Claim 5 has been amended as the Examiner suggested. In claim 6, "amphetamine" was recited twice. This has been corrected. It is believed that the claim amendments obviate the rejections.

The amendments of claims 1, 5, and 6 herein have been made to clarify the claims and do not narrow the scope of the claims. Accordingly, Applicants are entitled to a full range of equivalents upon issuance of the instant claims.

In view of the amendments to the claims, Applicants respectfully request withdrawal of the rejections of claims 1-9 under 35 U.S.C. § 112, second paragraph.

The 35 U.S.C. §103 Rejection of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagaoka et al. ("Beneficial Effects of a Serotonin-noradrenaline...", *Medicine and Drug Journal* 37 (10):238-240, October 1, 2001) or Horrobin et al. (WO 01/26623, published April 19, 2001) alone or in view of Iglehart, III (U.S. Patent No. 6,395,788) or Mendel et al. (CA 133:232864). This rejection is respectfully traversed.

Nagaoka discloses that administration of milnacipran led to an improvement in the self-reported mood and pain of a female patient diagnosed with fibromyalgia.

WO 01/26623 discloses a method of treating conditions of fatigue, pain, weakness, and depressed mood that are associated with neurological disorders, such as chronic fatigue syndrome, stroke, and fibromyalgia (abstract). The treatment involves administering a selective inhibitor of noradrenaline (norepinephrine) reuptake, together with phenylalanine or tyrosine (abstract).

The present application was filed on November 5, 2001. Nagaoka was published in October 2001. Accordingly it is only available as prior art under 35 U.S.C. § 102(a). WO 01/26623 was published on April 19, 2001. WO 01/26623 does not designate the United States, and so is not available as prior art under 35 U.S.C. § 102(e). It is only available as prior art under 35 U.S.C. § 102(a) as of its publication date. The Examiner is requested to consider the enclosed Declarations under Rule 131, submitted by the named co-inventors of the present application, Jay D. Kranzler and Srinivas Gandham Rao. In the declarations, they each declare that prior to April 19, 2001, the subject matter of the present application was invented in the United States. As evidence of conception or reduction to practice before April 19, 2001, they declare that they gave a presentation to representatives of Pierre Fabre before April 19, 2001, which concerned the use of milnacipran to treat fibromyalgia syndrome. Appended to the Declarations are slides from that presentation that disclose the use of milnacipran to treat fibromyalgia syndrome and the idea of trials of milnacipran to treat fibromyalgia syndrome. This demonstrates that the subject matter of the present claims was invented before April 19, 2001. Therefore, the Declarations are effective to remove Nagaoka and WO 01/26623 as prior art under 35 U.S.C. § 102(a).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the

prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the references or combine reference teachings so as to arrive at the claimed invention. Third, the art must provide a reasonable expectation of success. M.P.E.P. § 2143. The teaching or suggestion to arrive at the claimed invention and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure (M.P.E.P. § 2143, citing with favor *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Iglehart (U.S. Patent No. 6,395,788) discloses that administration of cyclobenzaprine is effective at treating sleep disturbance of patients who suffer from fibromyalgia and chronic fatigue syndrome, and that the patients also experienced relief from fatigue and diffuse pain (col. 4, lines 37-48). It discloses that the compositions to treat fibromyalgia and chronic fatigue syndrome can include cyclobenzaprine along with other therapeutic agents, including an atypical antidepressant (col. 7, line 63 to col. 8, line 2). Atypical antidepressants suitable for use in the compositions are disclosed to include serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, amoxapine, and maprotiline (col. 8, line 10-12).

Iglehart discloses the use of cyclobenzaprine, optionally together with an SNRI, to treat sleep disturbances associated with fibromyalgia. Iglehart does not disclose or suggest the use of milnacipran to treat fibromyalgia or its symptoms. In addition Iglehart does not disclose or suggest the use of any SNRI without the concomitant use of cyclobenzaprine. Thus, Iglehart does not provide a suggestion or motivation to modify its teachings to arrive at a method of treating fibromyalgia or its symptoms involving administering milnacipran, without requiring concomitant administration of cyclobenzaprine. Accordingly, Iglehart does not provide a suggestion or motivation to modify its teachings to arrive at the presently claimed invention.

Mendel et al. (CA 133:232864) discloses N,N,-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine-HCl (sibutramine), and closely related cyclobutyl compounds, for treating fibromyalgia or neuropathic pain. WO 00/56318, another reference by Mendel et al. that was listed by the Examiner along with CA 133:232864 in the references cited, also discloses the same compounds for use in treating fibromyalgia and neuropathic pain. It

discloses that sibutramine has a pharmacological profile which is unique amongst monoamine reuptake inhibitors (page 8, lines 4-5). It discloses that sibutramine inhibits the reuptake of all three monoamines, differentiating it from serotonin-noradrenaline reuptake inhibitors (page 8, lines 8-12). It discloses that this unique combination of pharmacological actions is what renders sibutramine and the other compounds disclosed effective in the treatment of neuropathic pain such as that associated with fibromyalgia (page 8, lines 12-15).

The Mendel references do nothing to remedy the deficiencies of Iglehart. The Mendel references disclose particular cyclobutyl compounds for treating fibromyalgia. Milnacipran is an unrelated cyclopropyl-based compound. The use of milnacipran is not disclosed or suggested by Mendel. In addition, in WO 00/56318, Mendel et al. teach that the effectiveness of sibutramine and the related compounds in treating neuropathic pain, including pain from fibromyalgia, is due to their "unique" ability to inhibit reuptake of all three monoamines—serotonin, dopamine, and norepinephrine (page 8, lines 4-15). This teaches away from the use of a serotonin-norepinephrine reuptake inhibitor, such as milnacipran, to treat fibromyalgia, since the serotonin-norepinephrine reuptake inhibitors do not inhibit reuptake of dopamine.

The enclosed Rule 131 Declarations remove Nagaoka and WO 01/26623 as prior art references. Iglehart and Mendel, separately or combined, do not provide a suggestion or motivation to modify reference teachings to arrive at a method of treating fibromyalgia syndrome (FMS) or physiological symptoms associated therewith in an animal subject, comprising administering to an animal subject suffering from FMS, an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof. Thus, the cited references do not establish a *prima facie* case of obviousness of the claimed invention. Therefore, withdrawal of the rejection of under 35 U.S.C. § 103(a) over Nagaoka or WO 01/26623 in view of Iglehart and Mendel is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 359-3261 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 27th day of December, 2002.

Dawn M. Pole
Name

Dawn M. Pole
Signature